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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/918,874	08/26/97	ASHKENAZI	A P1129

EXAMINER

HM22/0615

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ART UNIT	PAPER NUMBER
1646	17

DATE MAILED: 06/15/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 04/05/99

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 7-10, 14-19, 28-36 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 7-10, 14-19, 28-36 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-404-496/40517

1) Claims 7 to 10, 14 to 19 and 28 to 38 are pending in the instant application. Claims 7, 14 and 33 to 35 have been amended and claim 36 has been added as requested by Applicant in Paper Number 15, filed 05 April of 1999.

2) Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4) Claims 7 to 10, 14, 16 to 19, 28, 29 and 32 to 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant specification does not provide the guidance needed to make and use an "RTD" polypeptide comprising other than all or a specifically identified functional portion of the amino acid sequence presented in SEQ ID NO:1 of the instant application for those reasons of record in section 2 of Paper Number 12.

Applicant has traversed this rejection on the premise that 35 U.S.C. § 112, first paragraph, permits an artisan to present claims of essentially limitless breadth so long as the specification provides one with the ability to test any particular embodiment which is encompassed by the material limitations of a claim and thereby distinguish between those embodiments which meet the functional limitations from those embodiments which don't. This argument is not entirely without merit. However, the issue here is the breadth of the claims in light of the predictability of the art

as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. Applicant's 'make and test' position is inconsistent with the decisions in *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), was cited as the judicial basis for the instant rejection in the previous office action, *Amgen v. Chugai Pharmaceuticals Co. Ltd.*, 13 USPQ2d, 1737 (1990), and *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988). *In re Wands* stated that the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of this factors were addressed in the initial rejection. The text in lines 17 and 18 on page 11 of the instant specification states that the term "RTD polypeptide" encompasses "RTD variants". The text in lines 16 to 18 on page 12 indicates that the term "RTD variant" encompasses any "biologically active RTD as defined below having at least about 80% amino acid sequence identity with the RTD having the deduced amino acid sequence shown in Fig. 1A (SEQ ID NO:1) for a full-length native sequence human RTD". The text in lines 27 to 31 on page 16 states that "biologically active" means "having the ability to modulate apoptosis (either in an agonistic or stimulating manner or in an antagonistic or blocking manner) in at least one type of mammalian cell *in vivo* or *ex vivo*". The current claims encompass non-naturally occurring proteins having an amino acid sequence which deviates from the single naturally occurring amino

acid sequence disclosed in the instant specification by as many as 77 out of 386 amino acid residues. It is noted, however, that there in not a single example in the instant specification, working or prophetic, of an RTD polypeptide whose amino acid sequence deviates from nature. Since there are **no** working examples, then one must consider the guidance provided by the instant specification and the prior art of record. The instant specification provides absolutely no guidance as to which amino acid residues in SEQ ID NO:1 of the instant application are essential for the functional and structural integrity of an RTD polypeptide and which residues are either substitutable or expendable. Further, there is no functionally and structurally analogous protein which has been identified in the prior art for which this information is known and could be extrapolated to an RTD polypeptide by analogy. Applicant urges that the text on pages 18 to 20 of the instant specification provides the needed guidance. That text consists of nothing more than an invitation to experiment. It suggest known methods through which DNAs encoding addition proteins might be obtain an analytical methods through which critical residues could be identified. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required;

there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one can not following the guidance presented therein and practice the claimed method without first making a substantial inventive contribution. The instant claims encompass a vast, almost limitless, number of RTD polypeptides having non-naturally occurring amino acid sequences and yet the instant specification provides no working examples and no guidance that would permit and artisan to practice the invention commensurate with the scope of the instant claims.

Applicant's argument is based upon a premise that the standard under 35 U.S.C. ¶ 112, first paragraph, is that of mutating a subject protein and testing to see if it retains the desired biological activity is a position that has been routinely dismissed by the courts, as shown by those decisions cited above.

Further, *In re Wands* determined that the repetition of work which was disclosed in a patent application as producing a composition containing an antibody, which is a naturally occurring compound, did not constitute undue experimentation even if the antibody produced thereby was not identical to those that were disclosed in that application. The instant claims are not limited to naturally occurring compounds and the instant specification does not provide a description of a repeatable process of producing an RTD polypeptide whose amino acid deviates from the single disclosed, naturally occurring sequence by as much as 80%. To practice the

instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the amino acid sequence of SEQ ID NO:1 which are required for the functional and structural integrity of that protein. It is this additional characterization of that single disclosed, naturally occurring, protein that is required in order to obtain the functional and structural data needed to permit one to produce an RTD polypeptide which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

With regard to the propriety of specifically considering the decisions of *In re Fisher*, *Amgen Inc. v. Chugai*, and *In re Wands* to the exclusion of the plurality of decisions cited by Applicant in determining the patentability of the instant claims, Applicant is encouraged to review the discussion of 35 U.S.C. § 112, first paragraph in a recent CAFC decision, *Genentech, Inc. v. Novo Nordisk*, 42 USPQ2d, 100 (CAFC 1997), in which these three decisions were considered as the controlling precedents in determining enablement issues where protein and recombinant DNA issues are concerned. These decisions have been relied upon in the instant rejection and by the court because they show that the judicial interpretation of the first paragraph of 35 U.S.C. § 112 requires that the breadth of claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. To argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the

instant claims only encompass the working embodiments is judicially unsound. Unless one has a **reasonable expectation** that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are **more likely to work that not** without actually making and testing them then the instant application does not support the breadth of the claims. In the instant case it is highly improbable that any protein having ##% amino acid sequence identity to the disclosed protein will more likely than not perform in the manner disclosed and the instant specification does not provide the guidance needed to predictably alter that sequence with any reasonable expectation that the resulting protein will function as an RTD polypeptide.

Applicant has urged that the decision of *The Regents of the University of California v. Eli Lilly and Company,* 43 USPQ2d 1398 (CAFC 1997) is not applicable to the instant claims because "the state of the art has evolved such that with respect to the presently disclosed sequences, one skilled in the art can readily and predictably identify RTD polypeptides within the scope of the claims using for example, routine probing techniques". Applicant is advised that this decision has been cited in support of a rejection of the claims on the basis that the instant specification does not provide a **written description** of a nucleic acid encoding an RTD polypeptide having other than the amino acid sequence presented in SEQ ID NO:1 of the instant application. The "state of the art" has nothing to do with written description.

5) Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This claim requires a nucleic acid, which is a chemical entity, to hybridize to a "nucleotide sequence", which is a property of a nucleic acid and not a material entity in and of itself. Further, this claim appear to require a nucleic acid to encode an RTD polypeptide and to hybridize to a nucleic acid which also encodes an RTD polypeptide. The instant specification provide neither a description or the guidance needed to make a nucleic acid which encodes an RTD polypeptide and whose nucleotide sequence is complementary to the nucleotide sequence

6) Claims 7 to 10, 14 to 19 and 28 to 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6.1) Claims 7 to 10, 14 to 19 and 28 to 36 are vague and indefinite in the recitation of either of the terms "RTD polypeptide" or "tumor necrosis factor receptor homolog" for those reasons of record in section 4.1 of Paper Number 12. Applicant has traversed this rejection on the premise that the claims recite clear structural limitations. As stated in the original rejection these claims are vague because "it is not possible for a practitioner to determine if a polypeptide **which otherwise meets the material limitations of a claim** are included or excluded by either of these terms".

6.2) Claims 7 to 10, 14 to 19, 28 to 31 and 33 to 35 are vague and indefinite because they recite the terms "about" and "sequence identity" and the algorithm to be employed in the determination of the value of the term "sequence identity" has not been disclosed. Applicant has traversed this rejection on the basis that the text bridging pages 12 and 13 of the instant specification provides the guidance needed to interpret this limitation. This text does not provide the required degree of precision needed to interpret this limitation. As stated therein "Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill of the art". However, as illustrated in the original rejection, those different ways do not yield the same value for the same comparison.

6.3) Claims 36 is vague and indefinite because the term "hybridizes under stringent conditions" is a conditional property and neither the instant specification or the claim recites those conditions. There is no single set of hybridization conditions which are accepted in the art as "stringent conditions".

7) Applicant's arguments filed 05 April of 1999 have been fully considered but they are not persuasive.

8) Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached at (703) 308-2731.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN ULM
PRIMARY EXAMINER
GROUP 1800